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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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DATE SEP 25 1980

SUBJECT EPA Reg. No. 10182-EUP-15, PP 9G2154 and FAP 9H5201; Neurotoxicity Study with Pirimiphos-Methyl.

TOX Chem. #334B

FROM John Doherty, Ph.D. 9/11/80 9/15/80
Toxicology Branch/HED (TS-769)

TO Jay Ellenberger, PM #12 and Residue Chemistry Branch/HED
Registration Division (TS-767) (TS-769)

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Actions Requested:

Review acute delayed neurotoxicity study with pirimiphos-methyl as part of data requirements to support the safety of this new pesticide and consider the hazards associated with the subject EUP program.

Conclusion:

1. Toxicology Branch has decided to postpone a decision on the EUP program and tolerance requests until the several problems raised by Residue Chemistry Branch regarding tolerance levels and metabolites have been adequately resolved.

2. Toxicology Branch cautions that it will not be able to recommend in favor of a tolerance of greater than 20 ppm on peanuts because such levels would exceed the NOEL for cholinesterase effects.

3. The acute delayed neurotoxicity study submitted with this package (reviewed below) has been classified as Core Supplementary and cannot be used to fulfill the data requirement. A third study will have to be submitted (see remarks below).

Remarks:

1. The results of the neurotoxicity study revealed that hens treated with pirimiphos-methyl show an initial "ataxia" that results in the inability of the hens to stand up. This initial effect subsides after up to 6 days. However, during days 7-16 postdosing, ataxia again develops althouyh to a mild degree. Histopathology revealed increased incidences of lesions over that normally found in controls.

2. The testing laboratory asserts that although there were difficulties in correlating the neuropathological findings and clinical ataxia, the results suggest that at 51 and 102 mg/kg, pirimiphos-methyl is neurotoxic (p. 12 of report).

3. To clarify the issue, another study must be submitted that includes a second dosing 21 days following the first dose as per the proposed Guidelines published in 1978.

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The final report of the requested study must include the individual animal histopathology reports.

4. Pending the outcome of the repeat study, a 90-day subchronic feeding study with chickens and/or other studies may be required. The subchronic studies with chickens on file with EPA use only doses up to 48 ppm and continue feeding for up to 56 days. The doses of this future study, if eventually required, must be such that noticeable pharmacological effects are evident. The 48 ppm dose level used is not very much different from a NOEL for ChE in rats and dogs.

5. Toxicology Branch is of the opinion that neurotoxicity is a potentially serious hazard to man. Although the hen is the standard animal for testing because the rat, mouse and dog are not as susceptible, there is a possibility that the human is much more susceptible than the hen. Thus, the requirement for the additional neurotoxicity studie(s) is justified.

6. The terms of this request for an Experiment Use Permit provide that 715 gal. of ACTELLIC® 7E (5000 lbs. a.i.) be used to treat 125,000 tons (approximately) of peanuts in the state of Alabama (1,000 lbs.), Florida (800 lbs.), Georgia (1,600 lbs.), North Carolina (200 lbs.), New Mexico (200 lbs.), South Carolina (200 lbs.), Texas (800 lbs.) and Virginia (200 lbs.). The duration of this permit is limited to one year.

7. The product to be used (ACTELLIC® 7E) has been reviewed for labelling and inerts clearance (see the memo of February 21, 1980 concerning PP 9G2154 by J. Doherty).

Review of Study

Study Title: The acute oral toxicity (LD_{50}) and neurotoxic effects of pirimiphos-methyl on the domestic hen.

Laboratory: Huntingdon Research Centre, ICI Corporation, England. Study Date: June 20, 1980.

Part I - LD_{50} Determination

6 groups of 5 hens (over 12 months of age and of 2000-3000 gm body weight) were dosed by oral gavage with 0, 20, 36, 65, 117 or 210 mg/kg of test material (96.7% pirimiphos-methyl). A parallel set of six groups was similarly treated and was further treated with PAM (50 mg/kg) and atropine (10 mg/kg) intramuscularly. Fourteen days were allowed for observation following injections.

An unprotected LD_{50} of 80 (40-160) mg/kg with 95% confidence limits resulted.

A protected LD_{50} of 102 (64-163) mg/kg with 95% confidence limits resulted.

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The birds treated with pirimiphos-methyl were reported as being "quiet" after dosing. After day 1, the test birds were reported as being "unsteady". This unsteadiness, which was only reported in test birds receiving pirimiphos-methyl, is reported to have subsided after the fourth day. The severity of the unsteadyness was to the extent that many treated birds were unable to stand. Pirimiphos-methyl treated birds responded in this manner whether or not they were co-treated with PAM and atropine.

No histopathology was conducted on the birds surviving the acute LD_{50} tests.

Part II - Neurotoxicity

6 groups of 10 hens were dosed as follows:

Group No.	Compound	Dose Level (mg/kg)
1	Corn oil	0
2	TOCP	500
3	Pirimiphos-methyl	26x
4	"	51x
5	"	102x
6	"	102x

x all birds treated with pirimiphos-methyl were further treated with 50 mg/kg PAM and 10 mg/kg atropine intramuscularly.

Following injection, the birds were observed for 21 days prior to sacrifice.

Results:

Bird Health - The birds receiving 51 or 102 mg/kg of pirimiphos-methyl were unable to stand on days 1 and 2 following administration. Recovery from this initial toxic effect is reported as occuring by day 7. On days 7-17, there were frequent reports of ataxia noted. This ataxia is reported as not being the typical classical ataxia associated with TOCP. An ataxia index for total observations is as follows:

Group	Index
Control	0
TOCP	4.74
26 mg/kg	1.15
51 mg/kg	1.36
102 mg/kg	1.81
102 mg/kg	1.57

Index = total severity score (0-8)/total observations for pirimiphos-methyl. The initial ataxia (days 1-6) was not included. Ataxia for the TOCP groups was not noticed during days 1-6.

A dose dependent increase in ataxia is noted.

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The highest level of this ataxia (not including the initial response) is described as "slight-incoordination; occasional stumbling or wing dropping especially after exertion." Unlike the birds treated with TOCP, there were no signs of ataxia in the pirimiphos-methyl treated birds in the last 4 days of observation (days 17-21).

Gross Pathology - Two TOCP treated birds were reported to have "general atrophy of muscles". However, none of the pirimiphos-methyl treated birds were reported as having gross lesions in nerve or muscle tissue.

Histopathology - The following index of histopathological lesions was determined by Toxicology Branch reviewer.

Group	Index
Control	1.05
26 mg/kg	1.025
51	1.29
102	1.36
TOCP	3.00

Index = total severity of lesions/number of hens examined.

These data indicate an increase in histopathological lesions in the hens treated with the higher doses of pirimiphos-methyl.

Conclusion:

This test is Core Supplementary. It is evident that some kind of unusual ataxia not found in controls develops. Moreover, this is supported by dose related increases in histopathological findings. Although the results do not conclusively demonstrate a delayed neurotoxicity response that is characteristic of some organophosphates, this is a clear case where a second dose should have been given after the first 21 day observation period.

It is important to note the testing laboratory itself states that although there were difficulties in correlating the neuropathological findings and clinical ataxia, the results suggest that at 51 and 102 mg/kg pirimiphos-methyl is neurotoxic (see page 12 of the report).

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